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DAVID A. GAY
MCDERMOTT, WILL & EMERY
4370 LA JOLLA VILLAGE DRIVE
7TH FLOOR
SAN DIEGO, CA 92122

EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/779,376	FAN ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2005* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,9-16,19-23,26 and 30-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,9-16,19-23,26 and 30-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *14 November 2002* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on January 14, 2005 has been entered. The claims pending in this application are claims 5, 9-16, 19-23, 26, and 30-64. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 5, 13, 32, 39, 45, and 57 are rejected under 35 U.S.C. 102(e) as being anticipated by Barany *et al.,* (US Patent No. 6,027,889, filed on May 28, 1997).

Barany *et al.,* teach detection of nucleic acid sequence differences using coupled ligase detection and polymerase chain reactions.

Regarding claims 5, 32, 39, and 57, as shown in Figures 12-17, a first oligonucleotide probe having a target-specific portion and a 5' upstream primer-specific portion, and a second oligonucleotide probe having a target-specific portion and a 3' downstream primer-specific portion are hybridized adjacent to one another on a corresponding target nucleotide sequence and are ligated together in a ligase chain reaction. However, if there is a mismatch in ligation end of

the first or second probe, this mismatch will interfere with such ligation. Then unligated the first probe and the second probe are removed with Exo I and PCR-amplified using an upstream primer containing the same sequence as the 5' upstream primer-specific portion of the ligation product sequence (in the first probe) and a downstream primer complementary to the 3' downstream primer-specific portion of the ligation product sequence (in the second probe) wherein one primer has a detectable reporter label. Finally, PCR products are hybridized with a DNA array with different capture oligonucleotides immobilized at different particular sites and have nucleotide sequences complementary to the unique nucleotide sequences across the ligation junctions of given probe sets, and the labels of the PCR products captured on the DNA array at particular sites are detected as recited in steps f) and g) of claims 5, 32, 39, and 57 (see Figures 12-17 and columns 9, 10, 25-28, and 79-90). Note that: (1) the specification defines "universal priming site" as " a sequence of the probe that will bind a PCR primer for amplification" (see page 13, lines 14 and 15), the first probe and second probe taught by Barany *et al.,* are considered as first probe with the first and second portions and second ligation probe with the third, fourth, and fifth portions as recited in claims 5, 32, 39, and 57 (see attached Figure 12 with the examiner's handwritings); (2) since claims 5, 32, 39, and 57 do not require that step c) must perform before step d), Exo I digestion step in Figure 12 is considered as step c) recited in claims 5, 32, 39, and 57; (3) as shown in Figure 12, base G in left probe (a first ligation probe) that hybridizes to mutant sequence is considered as a first base at an interrogation position as recited in claim 5 and 39 or an interrogation position that is complementary to said detection position in a first ligation probe as recited in claim 32 and 57; and (4) according to the definition of "adaptor

sequence" (see page 19, third paragraph), the fifth portion of the second ligation probe (see attached Figure 12 with the examiner's handwritings) is considered to have an exogenous adaptor sequence as recited in claims 39 and 57 because the second ligation probe is synthesized *in vitro* and artificially made, and is exogenous to the target sequence.

Regarding claims 13 and 45, since Barany *et al.,* teach to amplify the ligation product by PCR and claims 13 and 45 are directed to basic PCR steps include repeated denaturation, annealing and extension, Barany *et al.,* disclose claims 13 and 45.

Therefore, Barany *et al.,* teach all limitations recited in claims 5, 13, 32, 39, 45, and 57.

Response to Arguments

In page 16, second paragraph bridging to page 17, third paragraph of applicant remarks, applicant argues that: (1) "[T]he five portions alleged to be shown in Figure 12 have been annotated to arbitrarily divide at most four discrete portions into a five arbitrary portions. Accordingly, the claims cannot be anticipated by Barany et al. because Barany et al. describes at most only four portions in the probes relied on by the Office"; (2) "[T]he adapters described by Barany et al. appear to correspond to a region within a target sequence, and more particularly, the adapters described by Barany et al. appear to correspond to a sequence that spans a ligation junction (see, for example, Office Action mailed January 29, 2003, pages 4-5, and Applicants' previous response at page 18)"; and (3) Barany *et al.,* do not teach that "the adapter sequence is specific to the claimed capture probe on the array and distinct from the target sequence".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since claims 5, 32, 39, and 57 do not describe the location of

fifth portion in first ligation probe or second ligation probe (ie., the fifth portion is located on 5' or 3' or middle of second ligation probe), in view of the attached Figure 12 with the examiner's handwritings, it is reasonable to consider that Barany *et al.*, teach the first, second, third, fourth, and fifth portion wherein the fifth portion is distinct from said first, second, third, or fourth portion (see attached Figure 12 with the examiner's handwritings). Second, applicant does not indicate what is the structural difference between the fifth portion recited in the claims and the fifth portion in the attached Figure 12 with the examiner's handwritings. Third, since Barany *et al.*, teach that PCR products are hybridized with a DNA array with different capture oligonucleotides immobilized at different particular sites (see attached Figure 12 with the examiner's handwritings and columns 25-27), Barany *et al.*, disclose contacting said amplicons with an array of capture probes as recited in step f) of claims 5, 32, 39, and 57. Since a PCR product contains an adaptor sequence (ie., the fifth portion) and forms a complex with a capture oligonucleotide in the array and an adaptor sequence (ie., the fifth portion) is not complementary to the target sequence (ie., mutant sequence, see the attached Figure 12 with the examiner's handwritings), Barany *et al.*, disclose that a capture probe of said array is specific to said adapter sequence and distinct from said target sequence as recited in step f) of claims 5, 32, 39, and 57. Note that the claims do not require that a capture probe specifically hybridize to said adaptor sequence.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 14-16, 34, 46-48, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.*, (1997) as applied to claims 5, 13, 32, 39, 45, and 57 above, and further in view of Walt *et al.*, (US Patent No. 6,327,410 B1, filed on September 11, 1998).

The teachings of Barany *et al.*, have been summarized previously, *supra.*

Barany *et al.*, do not disclose an array recited in claims 14-16, 34, 46-48, and 60.

Walt *et al.*, do teach an array comprising a substrate such as a fiber optical bundle recited in claims 16, 34, 48, and 60 with a patterned surface with discrete sites such as wells recited in claims 15 and 47, and a population of microspheres comprising at least a first subpopulation and a second subpopulation wherein said first subpopulation comprises a first nucleic acid and

second subpopulation comprises a second nucleic acid, and wherein said microspheres are randomly distributed on said surface such that said discrete sites contain microspheres recited in claims 14 and 46 (see Figures 7A and 7B, columns 3, 4, and 28-30).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 5 and 32 using an array recited in claims 14-16, 34, 46-48, and 60 in view of the patents of Barany *et al.*, and Walt *et al.*. One having ordinary skill in the art would have been motivated to do so because the simple replacement of one kind of nucleic acid array (ie., a regular oligonucleotide array taught by Barany *et al.*,) from another kind of nucleic acid array (an array with microspheres having immobilized nucleic acids taught by Walt *et al.*,) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement of one kind of nucleic acid array from another kind of nucleic acid array during the process of determining the identification of a nucleotide at a detection position in a target sequence would not change the method steps of the experiment since the array taught by Barany *et al.*, and the array taught by Walt *et al.*, are used for the same purpose (ie., a hybridization assay).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 18, first to third paragraphs of applicant's remarks, applicant argues that: (1) Barany *et al.,* do not teach that "the adapter sequence is specific to the claimed capture probe on the array and distinct from the target sequence"; and (2) "the cited references neither provide a suggestion or motivation to identify a nucleotide at a detection position in a target sequence using a fifth portion consisting of an adapter sequence that is specific to a capture probe and distinct from a target sequence. Absent such a suggestion or motivation, the claims cannot be obvious over the cited art".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since Barany *et al.,* teach that PCR products are hybridized with a DNA array with different capture oligonucleotides immobilized at different particular sites (see attached Figure 12 with the examiner's handwritings and columns 25-27), Barany *et al.,* disclose contacting said amplicons with an array of capture probes as recited in step f) of claims 5, 32, 39, and 57. Since a PCR product contains an adaptor sequence (ie., the fifth portion) and forms a complex with a capture oligonucleotide in the array and an adaptor sequence (ie., the fifth portion) is not complementary to the target sequence (ie., mutant sequence, see the attached Figure 12 with the examiner's handwritings), Barany *et al.,* disclose that a capture probe of said array is specific to said adapter sequence and distinct from said target

sequence as recited in step f) of claims 5, 32, 39, and 57. Note that the claims do not require that a capture probe specifically hybridize to an said adaptor sequence. Second, since, according to MPEP 2143.01 [R-2], "[O]bviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art", the motivation can only come from the cited references argued by applicant is incorrect. The examiner has provided motivation for above rejection and the motivation is in the knowledge generally available to one of ordinary skill in the art (see above office action under 35 U.S. C 103 (a)).

6. Claims 10, 13, 19-22, 26, 31, 33, 35, 42, 45, 49-52, 54, 56, 58, 59, and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.,* (1997) in view of Zhang *et al.,* (US Patent No. 5,876,924, filed on July 31, 1996).

The teachings of Barany *et al.,* have been summarized previously, *supra.* As shown in the rejection under 35 USC 102 (e), Barany *et al.,* teach claims 13 and 45.

Barany *et al.,* do not disclose step a) of claims 26, 33, 54, and 58, and claims 19-22, 31, 35, 42, 49-52, 59, and 61.

Regarding claims 10, 19-22, 26, 31, 33, 35, 42, 49-52, 54, 56, 58, 59, and 61, Zhang *et al.,* teach nucleic acid amplification method/hybridization signal amplification method. As shown in Figures 1 and 2, the two oligonucleotide probes (Capture/Amp-probe-1 and

Amp-probe-2) are first hybridized adjacent to one another on a corresponding target nucleotide sequence of the target nucleic acid in a sample wherein the Capture/Amp-probe-1 is 3'-biotinylated. Then the complex comprising target nucleic acid-probes is separated from any unbound reactants using streptavidin-coated paramagnetic beads as recited in claims 10, 19, 20, 31, 42, 49, 50, and 56 and the probes is ligated together in a ligation chain reaction. Ligated product of Capture/Amp-probe-1 and Amp-probe-2 are used as a template for PCR (see Figures 1 and 2, and columns 10-17). This method is used to detect a single mutation in a target (see column 6, first paragraph). Note that: (1) since claims 26, 33, 54, and 58 do not require that step a) must perform before step b), binding of target nucleic acid-probe complex to streptavidin-coated paramagnetic beads is considered to provide a support on which the target sequence is immobilized recited in step a) of claims 26, 33, 54, and 58; (2) Capture/Amp-probe-1 is considered to have a first portion and a second portion while AMP-PROBE-2 is considered to have third portion, fourth portion, and fifth portion (see attached Figure 1 with examiner's handwritings) wherein said exogenous adapter sequence is nested between said third and fourth portions of said second ligation probe as recited in claim 59; (3) streptavidin-coated paramagnetic beads are considered as a double-stranded moiety as recited in claims 10 and 42 since they bind to and separate the complex comprising target nucleic acid-probes which is double stranded from any unbound reactants; (4) the target nucleic acid is considered to be indirectly immobilized on streptavidin-coated paramagnetic beads as recited in claims 19, 21, 49, and 51; (5) biotinylated Capture/Amp-probe-1 is considered as a functional attachment moiety recited in claims 22, 52, and 61 since this probe attaches the target nucleic acid to

streptavidin-coated paramagnetic beads in the target nucleic acid-probe complex; and (6) a base located in 5' of capture/AMP-probe is considered as an interrogation position as recited in claims 26, 33, 54, and 58 (see Figure 1).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 10, 13, 19-22, 26, 31, 33, 35, 42, 45, 49-52, 54, 56, 58, 59, and 61 in view of the patents of Barany *et al.*, and Zhang *et al.*. One having ordinary skill in the art would have been motivated to do so because the simple replacement of one well known LDR/PCR method (LDR/PCR method of Barany *et al.*,) from another well known LDR/PCR method (LDR/PCR method of Zhang *et al.*,) in order to make hybridization probes (ie., a plurality of amplicons in step f) of claims 26, 33, 54, and 58) during the process for performing the methods recited in claims 26, 34, 54, and 58 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since LDR/PCR method of Zhang *et al.*, and LDR/PCR method of Barany *et al.*, are equivalent methods and are used for the same purpose (ie., producing hybridization probes).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 18, last paragraph bridging to page 20, second paragraph of applicant's remarks, applicant argued that: (1) "neither Zhang et al. alone, or Zhang et al. in view of Barany et al., teach or suggest a first and a second ligation probe having the five portions as claimed. Accordingly, the cited references fail to teach or suggest all the elements of the claimed invention and cannot provide a basis for a *prima facie* case of obviousness"; and (2) [R]eliance on a ligation step for alleging that the principle operation is unchanged fails to recognize that the alleged combination would require substantial reconstruction and redesign of the elements shown in the primary reference to Zhang et al. as well as a change in the basic principle under which Zhang et al. was designed to operate. The ligation steps of Barany et al. and Zhang et al. operate at different steps and apply different hybridization characteristics. For example, the hybridization specificity required to detect an amplification product (Barany et al.) differs from the hybridization specificity required to detect a target sequence (Zhang et al.). As such, the ligation step performs different and separate functions in each method within the cited references".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, Barany *et al.*, do teach a ligation probe comprising a first portion and a second portion or a third portion, a fourth portion, and fifth portion (see above

Response to Arguments to the rejection under 35 USC 102 (e)). Second, although this rejection is based on modifying the method of Barany *et al.*, the modification would not alter the principle operation because the rejection is based on that the simple replacement of one well known LDR/PCR method (LDR/PCR method of Barany *et al.*,) from another well known LDR/PCR method (LDR/PCR method of Zhang *et al.*,) in order to make hybridization probes. Since LDR/PCR method of Zhang *et al.*, and LDR/PCR method of Barany *et al.*, are used for the same purpose (ie., producing hybridization probes), they are equivalent methods and "the ligation step performs different and separate functions in each method within the cited references" argued by applicant is incorrect.

7. Claims 11, 12, 43, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.*, (1997) in view of Zhang *et al.*, (1996) as applied to claims 10, 13, 19-22, 26, 31, 33, 35, 42, 45, 49-52, 54, 56, 58, 59, and 61, and further in view of Gebeyehu *et al.*, (US Patent No. 4,921,805, published on May 1, 1990).

The teachings of Barany *et al.*, and Zhang *et al.*, have been summarized previously, *supra*.

Barany *et al.*, and Zhang *et al.*, do not disclose that said double-stranded specific moiety is an intercalator attached to a support wherein said support is a bead as recited in claims 11, 12, 43, and 44.

Gebeyehu *et al.*, teach to use an intercalator attached to a bead to separate non-hybridized probes from hybridized probes (see column 3, lines 39-54 and claims 1-10 in columns 12-14).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have removed non-hybridized probes using methods recited in claims 11, 12, 43, and 44 in view of the prior art of Barany *et al.*, Zhang *et al.*, and Gebeyehu *et al.*. One having ordinary skill in the art would have been motivated to do so because Gebeyehu *et al.*, have successfully separated non-hybridized probes from hybridized probes using an intercalator attached to a bead and the simple replacement of one well known nucleic acid separation method (based on the interaction between a ligand on a target nucleic acid with its binding partner) from another well known nucleic acid separation method (based on the interaction between a double nucleic acid probe with an intercalator) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the nucleic acid separation method taught by Zhang *et al.*, and the nucleic acid separation method taught by Gebeyehu *et al.*, are equivalent methods and are used for the same purpose (ie., removing non-hybridized probes).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

8. Claims 9, 23, 30, 41, 53, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.,* (1997) in view of Zhang *et al.,* (1996) as applied to claims 10, 13, 19-22, 26, 31, 33, 35, 42, 45, 49-52, 54, 56, 58, 59, and 61, and further in view of Seradyn Particle Technology (November 1996, pages 1-7).

The teachings of Barany *et al.,* and Zhang *et al.,* have been summarized previously, *supra.*

Seradyn Particle Technology (page 7) confirms that streptavidin-coated paramagnetic beads taught by Zhang *et al.,* comprise a plastic material as recited in claims 23, 30, 53, and 55 since these beads has polystyrene core.

Barany *et al.,* Zhang *et al.,* and Seradyn Particle Technology do not disclose that the target sequence is labeled with a binding ligand as recited in claims 9 and 41. However, Zhang *et al.,* teach steps b) to d) in claims 9 and 41 except the probe, not the target sequence, is labeled with a binding ligand in step a) (see column 8 and 10-13).

However, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have removed non-hybridized probes using a method recited in claim 9 or 41 in view of the prior art of Barany *et al.,* Zhang *et al.,* and Seradyn Particle Technology. One having ordinary skill in the art would have been motivated to do so

because a method for labeling different nucleic acids with a binding ligand was known in the art at the time the invention was made and the simple replacement of one well known nucleic acid separation method (based on the interaction between a ligand on a target nucleic acid with its binding partner taught by Zhang *et al.,*) from another well known nucleic acid separation method (based on the interaction between a ligand on a nucleic acid probe with its binding partner) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since using different methods to remove non-hybridized probes would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

9. Claim 37 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.,* (1997) in view of Zhang *et al.,* (1996) as applied to claims 10, 13, 19-22, 26, 31, 33, 35,

42, 45, 49-52, 54, 56, 58, 59, and 61 above, and further in view of Monforte *et al.*, (US Patent No. 5,830,655, published on November 3, 1998).

The teachings of Barany *et al.*, and Zhang *et al.*, have been summarized previously, *supra.*

Barany *et al.*, and Zhang *et al.*, do not disclose that said target sequence is attached to said support by direct chemical attachment of said target sequence to said support as recited in claims 37 and 63.

Monforte *et al.*, teach to immobilize nucleic acid templates by attachment to a solid support before a primer extension assay. Immobilization is via a covalent or non-covalent linkage (see last paragraph of column 6 and claims 1-3 in column 63).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 37 or 63 by attaching target sequences onto a solid support in view of the patents of Barany *et al.*, Zhang *et al.*, and Monforte *et al.*. One having ordinary skill in the art would have been motivated to do so because Monforte *et al.*, have successfully attached nucleic acid templates to a solid support before amplification of the nucleic acid templates and the immobilization of the nucleic acid templates to a solid support would enhance to separate hybridized complexes formed by the nucleic acid templates and hybridized probes from unhybridized probes and the simple replacement of one well known nucleic acid separation method (based on the interaction between a ligand on a target nucleic acid with its binding partner that immobilizes on a solid support taught by Zhang *et al.*,) from another well known nucleic acid separation method (based on the

interaction between ligation probes with target sequences immobilized on a solid support) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the nucleic acid separation method taught by Zhang *et al.*, and the nucleic acid separation method taught by Monforte *et al.*, are equivalent methods and are used for the same purpose (ie., removing non-hybridized probes).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

10. Claims 36 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.*, (1997) in view of Zhang *et al.*, (1996) and further in view of Monforte *et al.*, (1998) as applied to claims 10, 13, 19-22, 26, 31, 33, 35, 37, 42, 45, 49-52, 54, 56, 58, 59, 61, and 63 above, and further in view of Brown *et al.*, (US Patent No. 5,807,522, published on September 15, 1998).

The teachings of Barany *et al.*, Zhang *et al.*, and Monforte *et al.*, have been summarized previously, *supra.*

Barany *et al.*, Zhang *et al.*, and Monforte *et al.*, do not teach that said target sequence is attached to said support by absorption of said target sequence on said support wherein said support comprises charged groups as recited in claims 36 and 62.

Brown *et al.*, teach to immobilize nucleic acids onto a support comprising charged groups (ie., a slide with a layer of poly-l-lysine) (see column 16).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 36 or 62 by attaching target sequences taught by Zhang *et al.*, onto a solid support comprising charged groups in view of the patents of Barany *et al.*, Monforte *et al.*, and Brown *et al.*. One having ordinary skill in the art would have been motivated to do so because, due to interaction between negative charges of the nucleic acids and positive charges of the support, immobilization of nucleic acids onto a solid support comprising positive charged groups would increase efficiency of the immobilization and the simple replacement of one solid support (ie., the support taught by Monforte *et al.*) from another solid support (ie., the support with positive charges taught by Brown *et al.*) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since attaching target sequences onto a solid support comprising positive charged groups would enhance absorption of the target sequence on the support due to charge interaction.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

11. Claims 38 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.,* (1997) in view of Zhang *et al.,* (1996) and further in view of Monforte *et al.,* (1998) as applied to claims 10, 13, 19-22, 26, 31, 33, 35, 37, 42, 45, 49-52, 54, 56, 58, 59, 61, and 63 above, and further in view of Johnson *et al.,* (US Patent No. 6,372, 813, published on June 25, 1999).

The teachings of Barany *et al.,* Zhang *et al.,* and Monforte *et al.,* have been summarized previously, *supra.*

Barany *et al.*, Zhang *et al.,* and Monforte *et al.,* do not teach that said target sequence is attached to said support by photocrosslinking said target sequence to said support as recited in claim 36.

Johnson *et al.,* teach to photocrosslink a nucleic acid onto a solid support (see example 5, column 21).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 38 or 64 by attaching target sequences onto a solid support by photocrosslinking in view of the patents of Barany *et al.*, Zhang *et al.*, Monforte *et al.*, and Johnson *et al.*. One having ordinary skill in the art would have been motivated to do so because Johnson *et al.*., have successfully photocrosslinked a nucleic acid onto a solid support and the simple replacement of one well known nucleic acid immobilization method (an immobilization method taught by Monforte *et al.*,) from another well known nucleic acid immobilization method (an immobilization method taught by Johnson *et al.*,) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the nucleic acid immobilization method taught by Monforte *et al.*, and the nucleic acid immobilization method taught by Johnson *et al.*, are equivalent methods and are used for the same purpose (ie., nucleic acid immobilization).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 20, third paragraph bridging to page 21, first paragraph of applicant's remarks, applicant argues that "[A]s set fourth above, neither Barany et al. in view of Walt nor Zhang et al. in view of Barany et al. provide all the elements of the claimed invention or a motivation to combine the respective references. Accordingly, the independent claims are unobvious over the cited combination of references. The above tertiary references are cited allegedly for describing a further element found within the dependent claims. Because the cited art fails to describe each and every element of the claimed invention and because the tertiary references are directed to further elements within the dependent claims, the citations to Gebeyehu et al., Seradyn Particle Technology, Monforte et al. or Johnson et al. cannot cure the deficiencies of the primary and secondary references. Accordingly, the cited art cannot teach or suggest each and every element of the claimed invention".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Since Barany *et al.,* in view of Zhang *et al.,* do teach a ligation probe comprising a first portion and a second portion or a third portion, a fourth portion, and fifth portion (see above Response to Arguments to the rejection on claims 10, 13, 19-22, 26, 31, 33, 35, 42, 45, 49-52, 54, 56, 58, 59, and 61 under 35 USC 103 (a)), the citations to Gebeyehu et al., Seradyn Particle Technology, Monforte et al. or Johnson et al. are not used to cure the deficiencies of the primary and secondary references.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. No claim is allowed.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
April 15, 2005

FRANK LU
PATENT EXAMINER